# Cyber-Medical Systems

## Requirements, Components and Design

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# Outline

- **Introduction**
  - **Trends in Engineering and Medicine**
  - Examples from the medical practice
- Cyber-medical systems
  - Sensors
  - Circuits and architectures
  - Systems
- Conclusions

# The megatrends

- ▲ Relentless growth of computing, storage and communication technologies
  - ▽ Inexpensive terminals providing ubiquitous services
- ▲ Biomedical sciences becoming more quantitative
  - ▽ Societal need of better care at lower costs
- ▲ Big data issues fueling research and businesses
  - ▽ Models, algorithms, architectures to tame data deluge

**PRECISION MEDICINE**

# What is health?

World Health Organization

State of complex physical, mental and social well-being and not merely the absence of disease or infirmity

# Where medicine and engineering meet

- Data acquisition chains
  - Sequencing DNA, sensing proteins, …
- Data elaboration and transmission means
  - Telemedicine, robotics surgery
- Prosthetics, smart implants
  - Sensing, elaborating and actuating
- Drug dispensing
  - Off-body, on-body, in-body

# Cyber-medical systems
## objectives

- Bettering **medicine** by electronic means
- Bringing **low-cost** medicine to the people
- Exploiting electronic **well-being** as a **lifestyle**



# Cyber-medical systems
## objectives

- Bettering **medicine** by electronic means
- Bringing **low-cost** medicine to the people
- Exploiting electronic **well-being** as a **lifestyle**
- Opportunities:
  - Synergy of integrated **electronic and sensing**
  - **Platform-based design** of electro-sensing systems
  - **Connectivity**: mobile telephony as backbone

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# Point of care

- ▲Some molecular tests can be done in real time
  - ▽Efficient and lower cost for routine care
  - ▽Some diagnostics require multiple tests

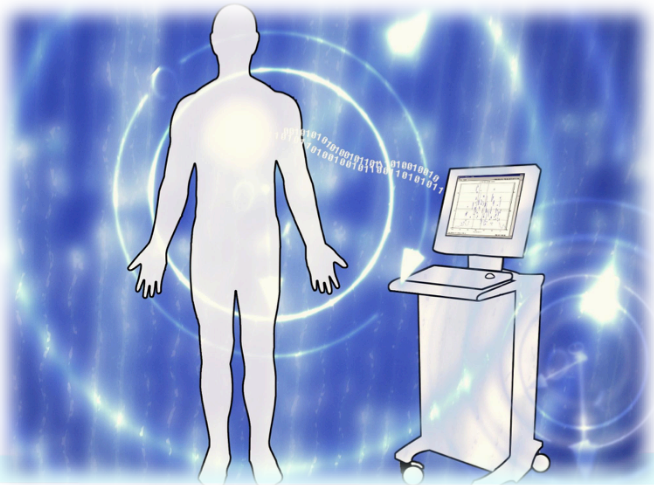
- ▲Emergency situations require real-time measures
  - ▽Patient's fluids are often connected
  - ▽Local tests and remote diagnosis

# Tele-medicine:
# Monitoring chronic patients

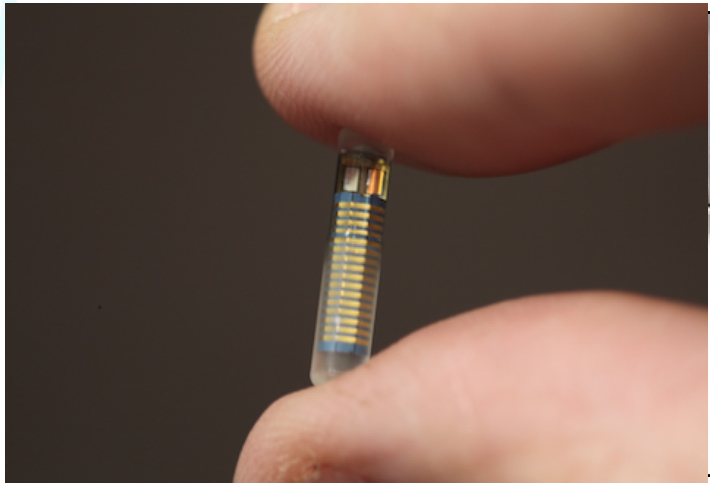
- Non-invasive monitors
  - Heart rate, $SpO_2$, blood pressure

[Courtesy: Smartcardia]

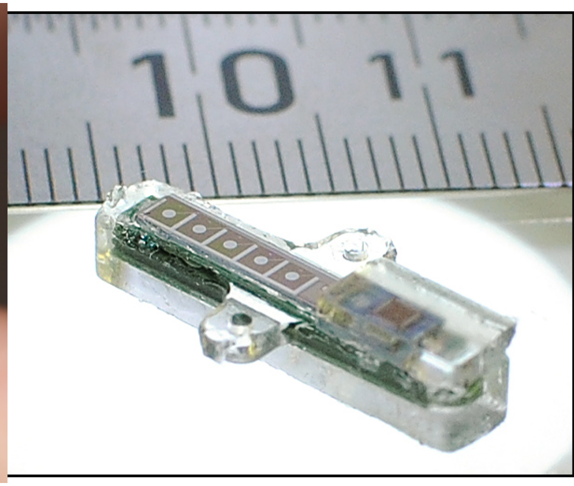
- Invasive monitors:
  - Metabolites: glucose, lactate, cholesterol
  - Continuous measurements calibrated in $T$ and $pH$
- Wireless challenges
  - Secure transmission
  - Remote powering



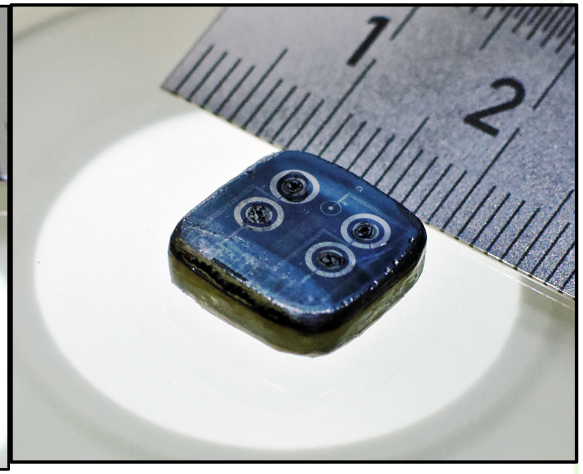
# Examples



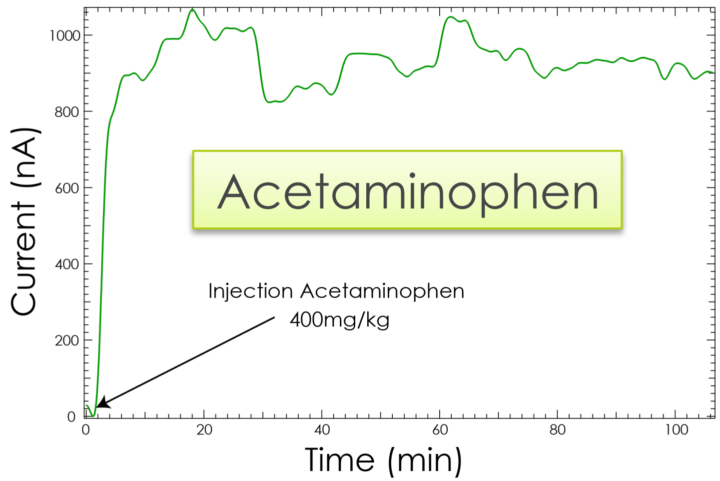
GLUCOSE SENSOR [Senseonics™ ]



Prototype for human implant [EPFL]

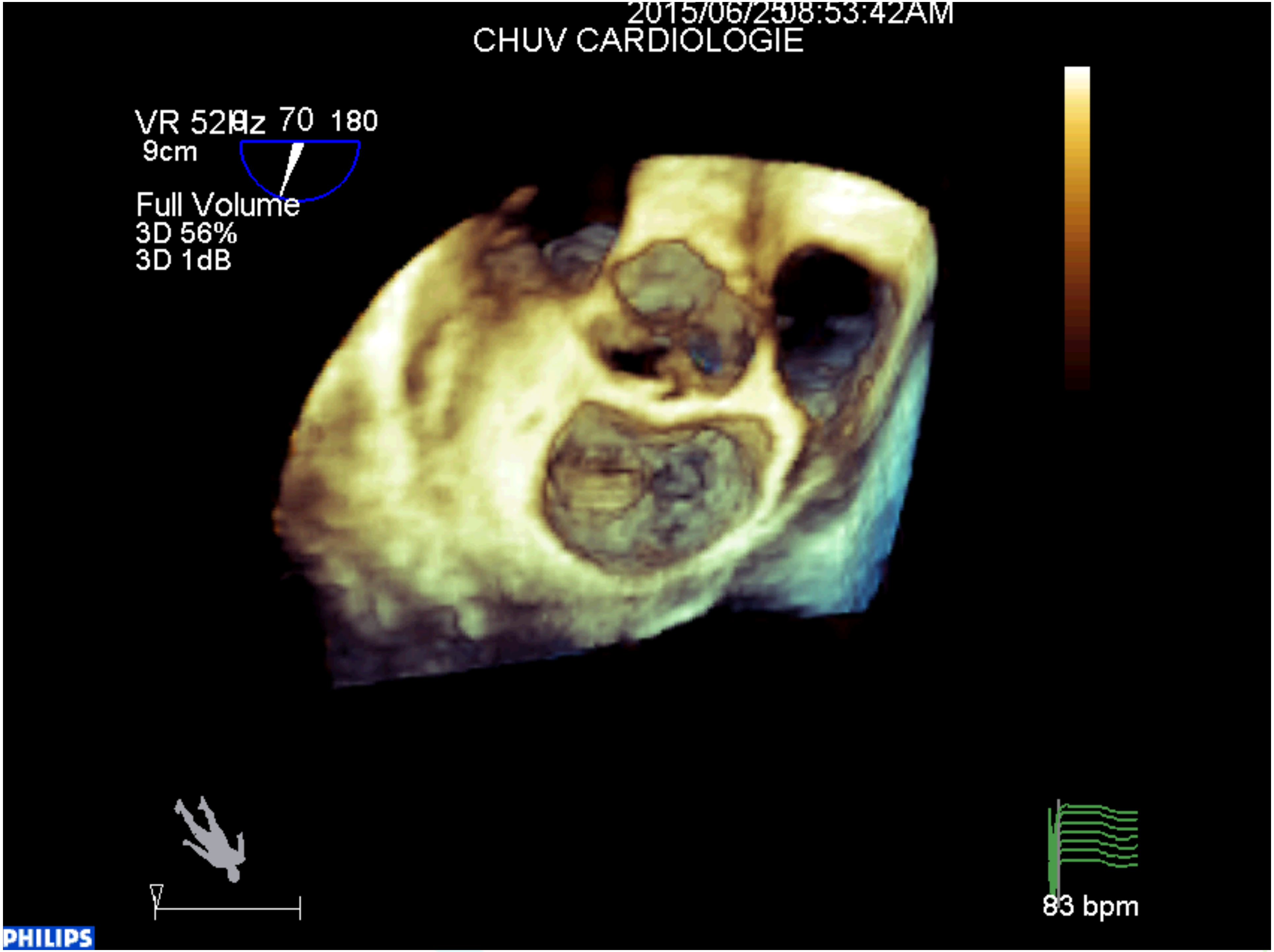


Muti-sensor for lab animals [EPFL]



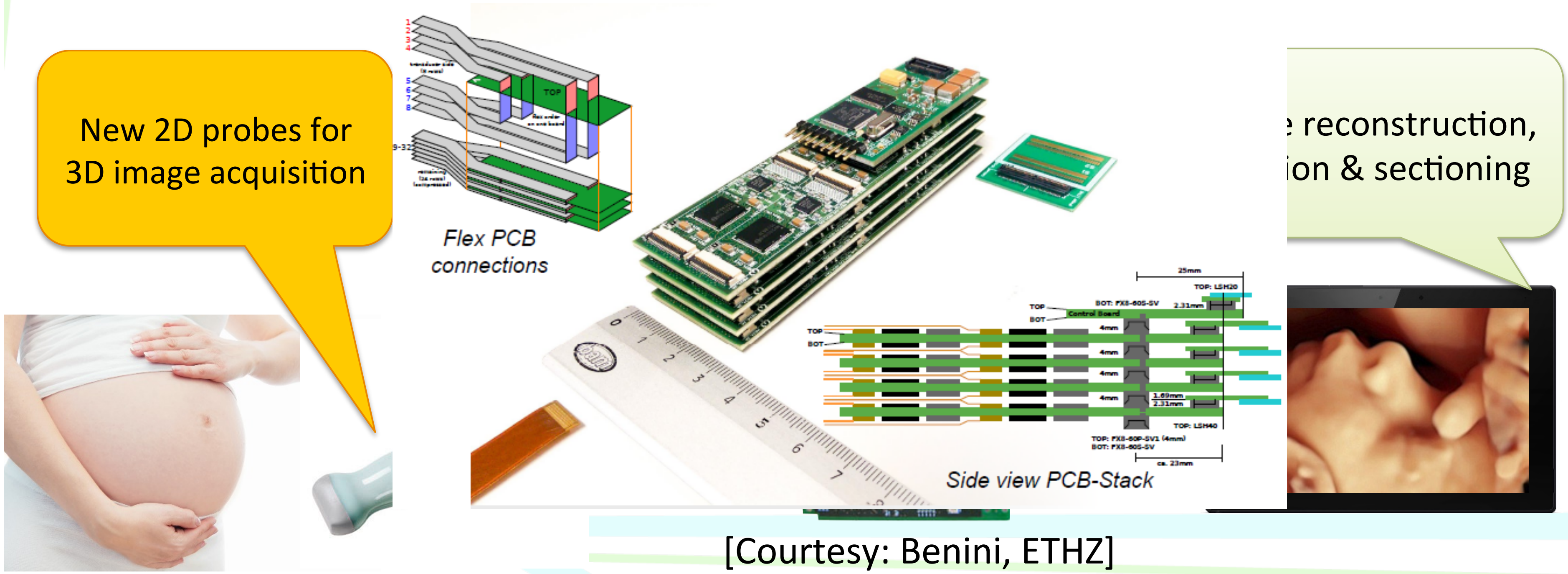

# Tele-medicine
# Remote ultrasound diagnosis

- ▲Ultrasound (US) imaging is widely used
  - ▽Standard US needs a radiologist to operate the probe
  - ▽Hard to use in emergencies and in remote areas
- ▲3D Ultrasound can obviate this problem
  - ▽3D volumes can acquired by non-specialist
  - ▽Then transmitted to medical provider
  - ▽Then sectioned and analyzed remotely
- ▲Current 3D systems are bulky, expensive and power-hungry


CHUV CARDIOLOGIE
70 180
9cm
Full Volume
3D 56%
3D 1dB
83 bpm

# Tele-medicine
# Remote ultrasound diagnosis

- Design portable 3D US system
  - Lightweight, low-power, wirelessly connected
- Tight integration of probe and beamforming electronics
  - High processing power
  - Heat removal




[Courtesy: Benini, ETHZ]

# Patient care support systems

- Drug administration *decision support systems*
  - Drug selection, dosage and timing
- Data acquisition by integrated sensors
  - Continuous and real-time
- Applicable to hospital care
  - In the future will enable also remote care

# Smart drug administration

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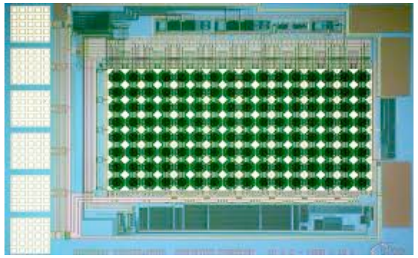
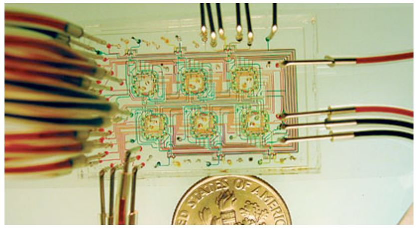
# Technologies



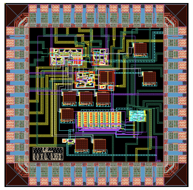
▲ Sensing

▽ Electrical, mechanical, optical



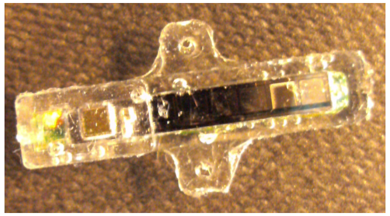
▲ Fluidics and transducers

▽ Micro tubes, valves, pumps



▲ Data acquisition electronics

▽ Discrete, integrated, monolithic with sensor



▲ Packaging

▽ Rigid/flexible, bio-compatible

# Biosensing targets

- Endogenous metabolites:
  - Glucose, lactate, cholesterol…
- Exogenous metabolites:
  - Drugs, e.g., anti-inflammatory, chemotherapy, …
- Biomarkers:
  - Tumor growth factors
- DNA, RNA
- Ions (K, Na)
- …

# Integrated sensors sensitivity and range

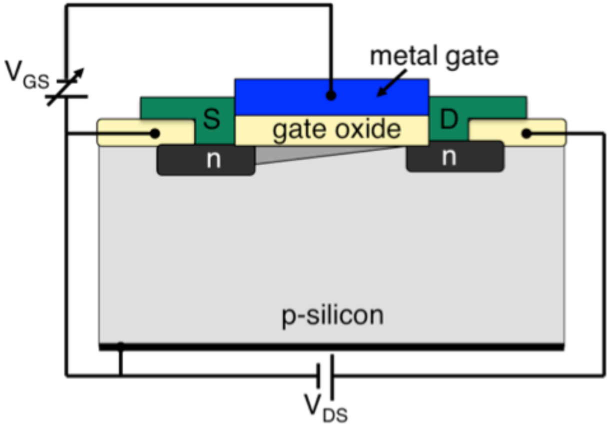
## Some endogenous metabolites

| Metabolite | Sensitivity ($\mu A/mM\ cm^2$) | Range (mM) | Detection limit ($S/N = 3\sigma$) ($\mu M$) |
|---|---|---|---|
| **Glucose** | 27.7 | 0.5 – 4 | 73 |
| **Lactate** | 40.1 | 0.5 – 2.5 | 28 |
| **Glutamate** | 25.5 | 0.5 – 2 | 195 |
| **ATP** | 3.42 | 0.5 – 1.4 | 208 |

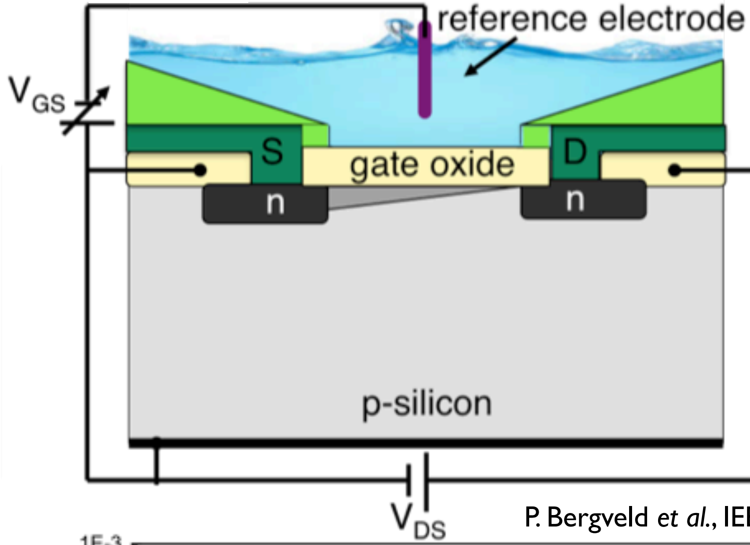
[Courtesy Carrara, EPFL]

# FETs: electronic transducers for chemi/bio-recognition events

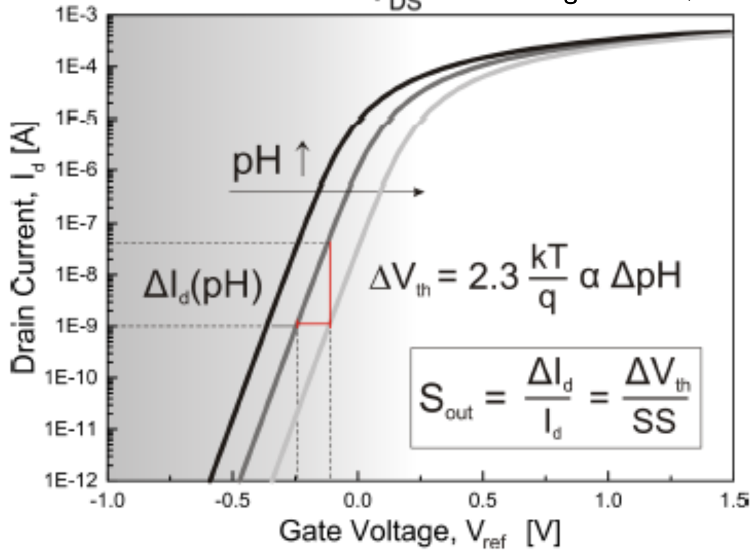
**MOSFET**




**ISFET**

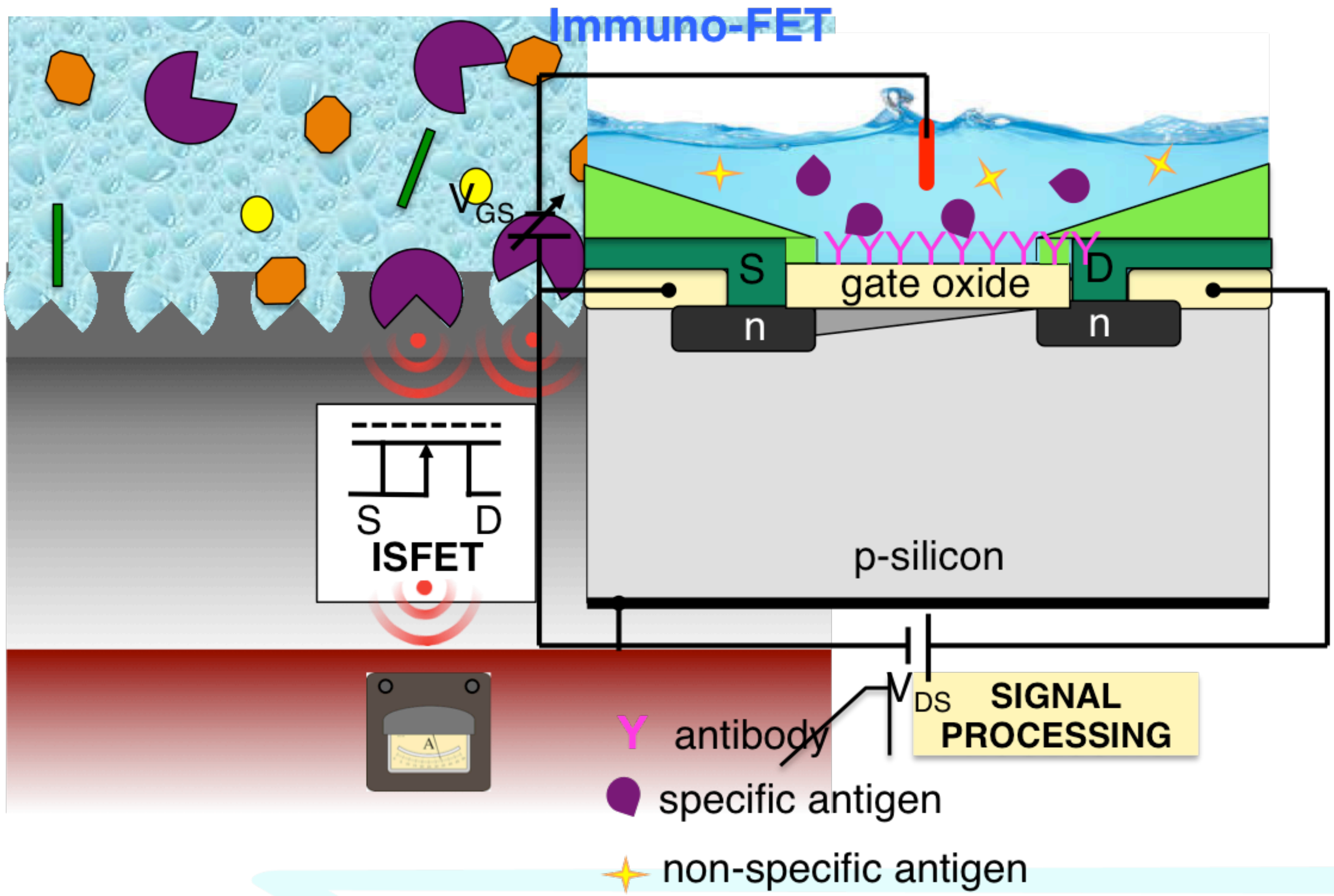



P. Bergveld *et al.*, IEEE TBME 17(1), 1970




- Surface potential changes as a function of the ion concentration:
  - pH sensing ($H^+$ ions)
  - Other ions (membrane)

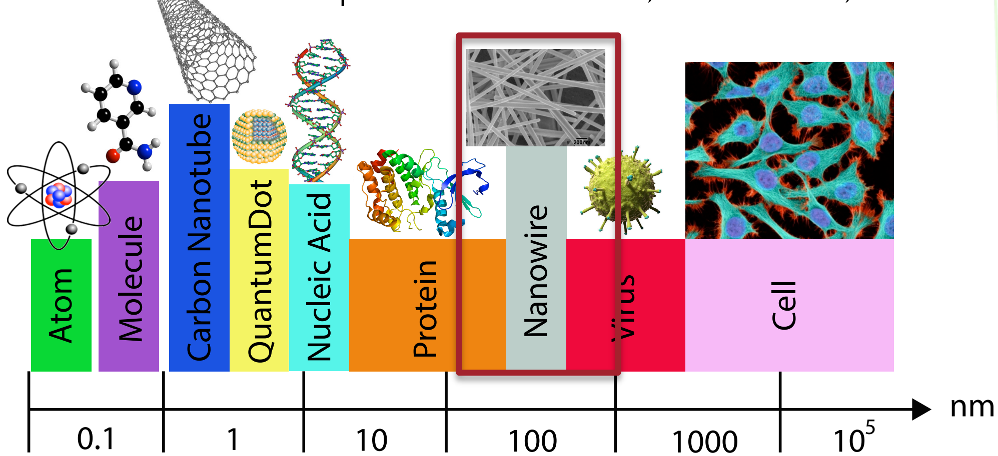
# Bio-FETs



Immuno-FET
V
GS
S
gate oxide
D
n
n
p-silicon
S
D
ISFET
V
DS
SIGNAL
PROCESSING
antibody
specific antigen
non-specific antigen

# Relevance of SiNWs

Reprinted from Curreli *et al.*, IEEE TNANO 7, 2008




## 1. Nano size

- Best interface to proteins

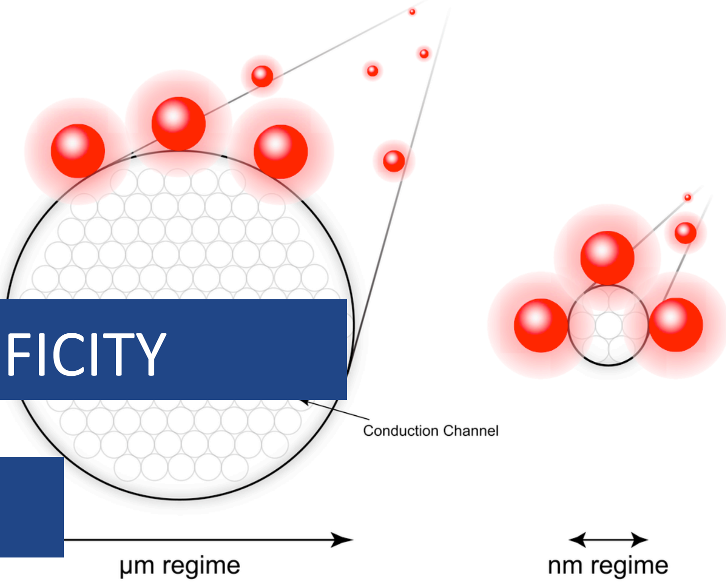
**SENSITIVITY**

## 2. Surface-to-volume ratio

- Larger interaction area
- Charge confinement

## 3. Silicon biomodification

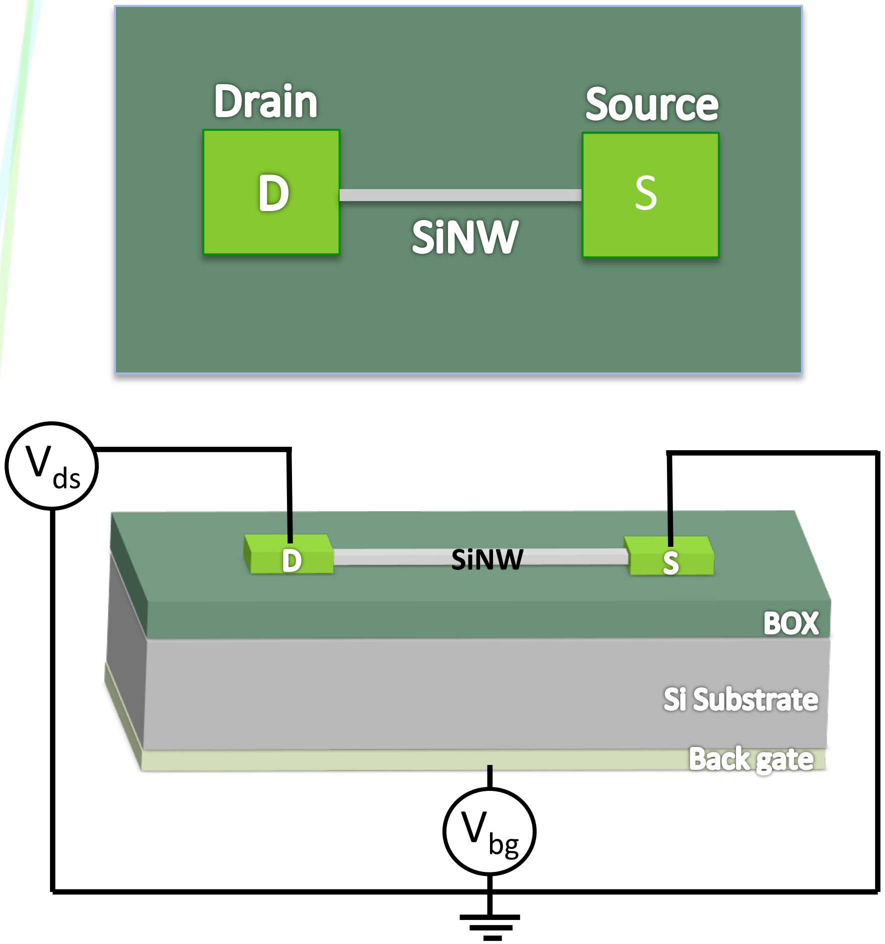
→ **SPECIFICITY**

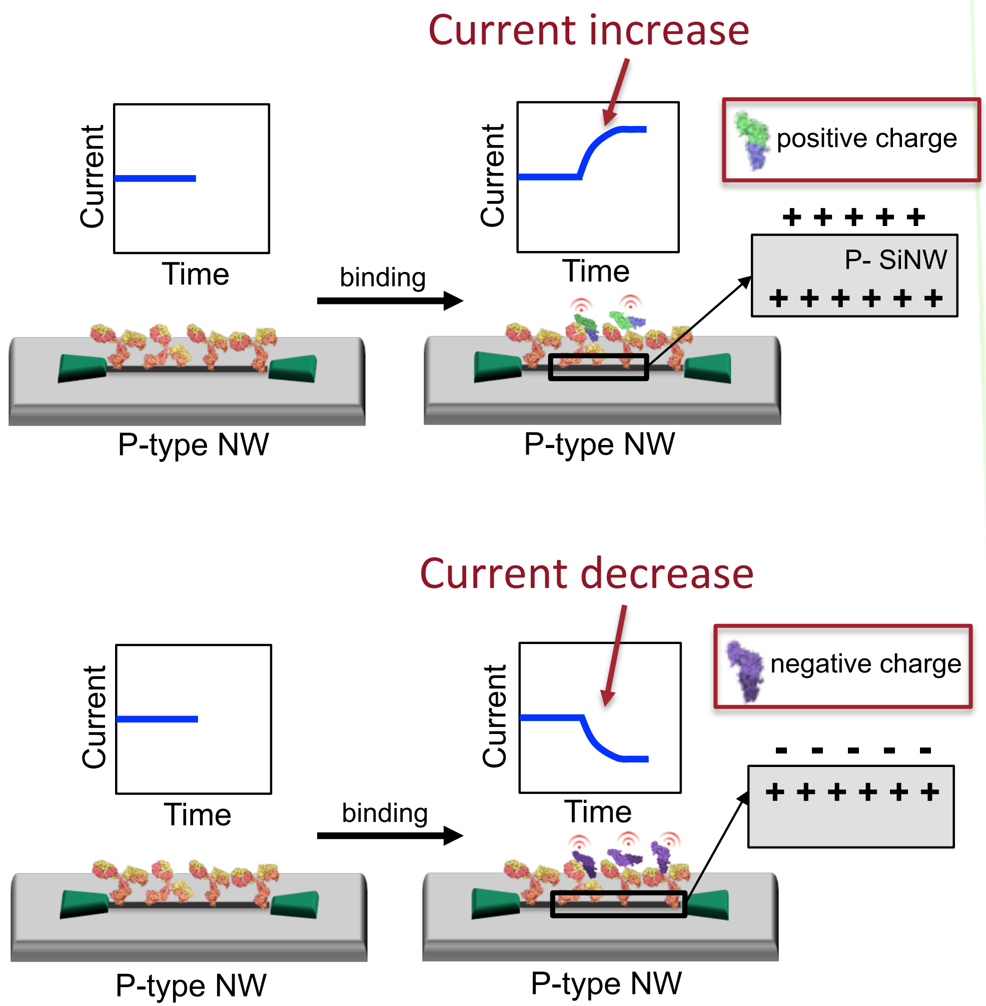



## 4. Compatibility

→ **INTEGRATION**

# SiNW-FETs for Biosensing

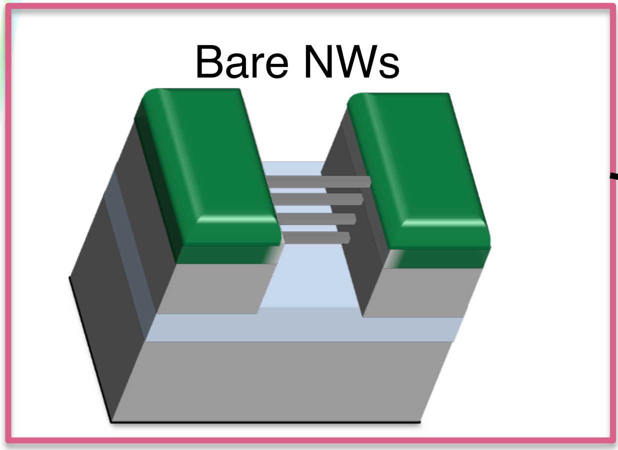


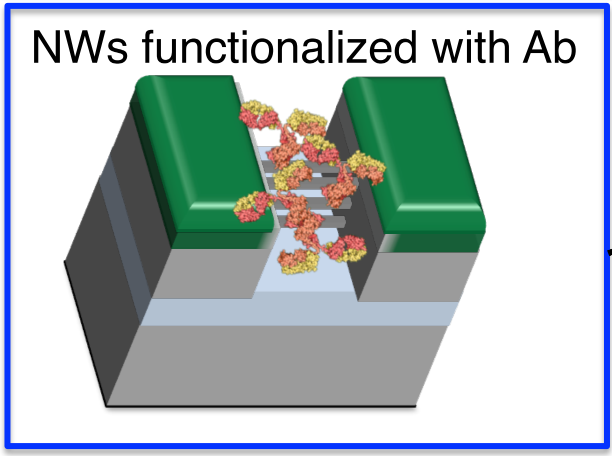





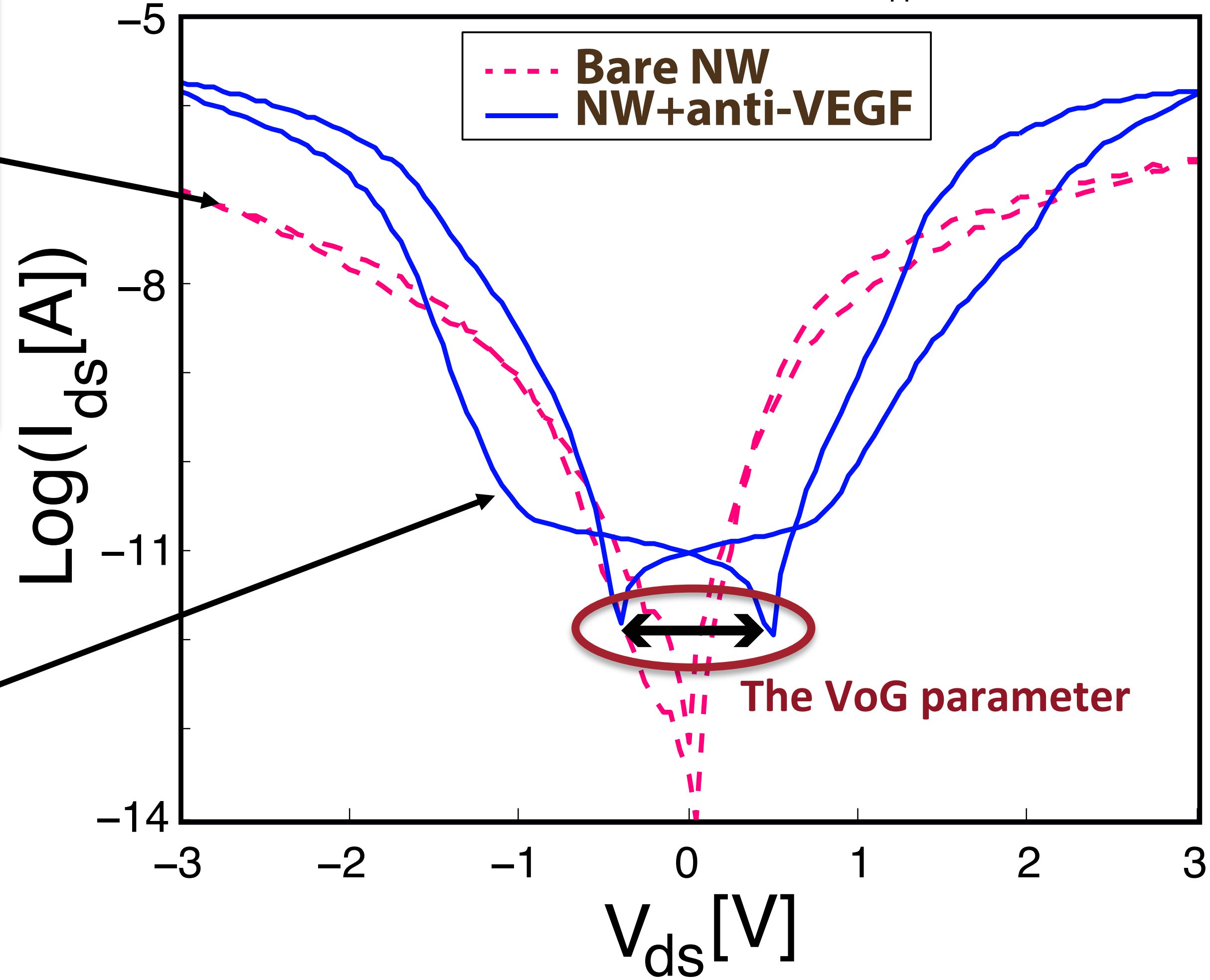

Reprinted from Patolsky *et al.*, PNAS 101(39), 2004

# Voltage-gap SiNW biosensors



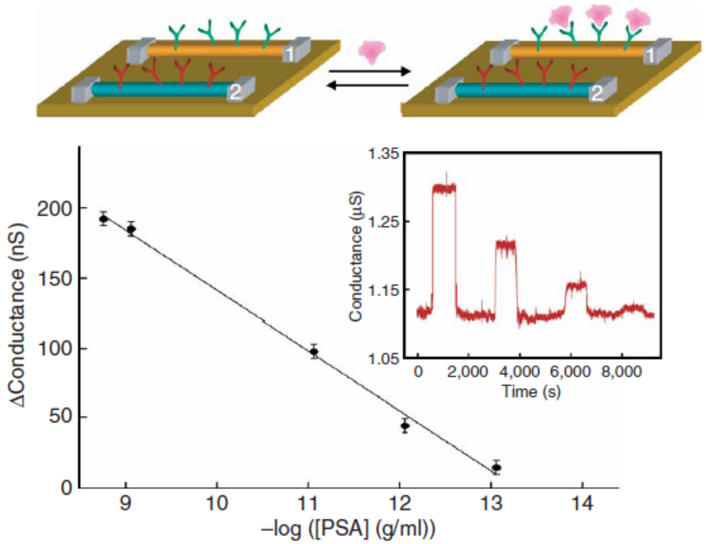




Puppo *et al.* BIOCAS 2014



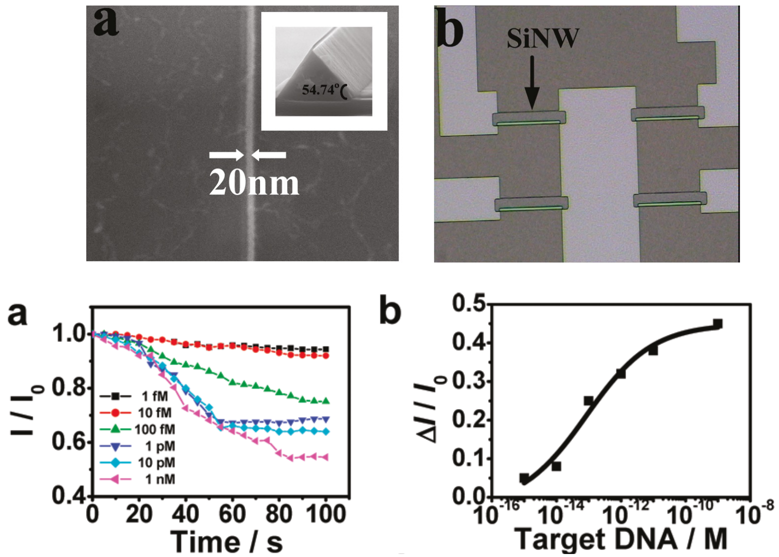
# Applications of Bio SiNW-FETs

## Cancer markers detection



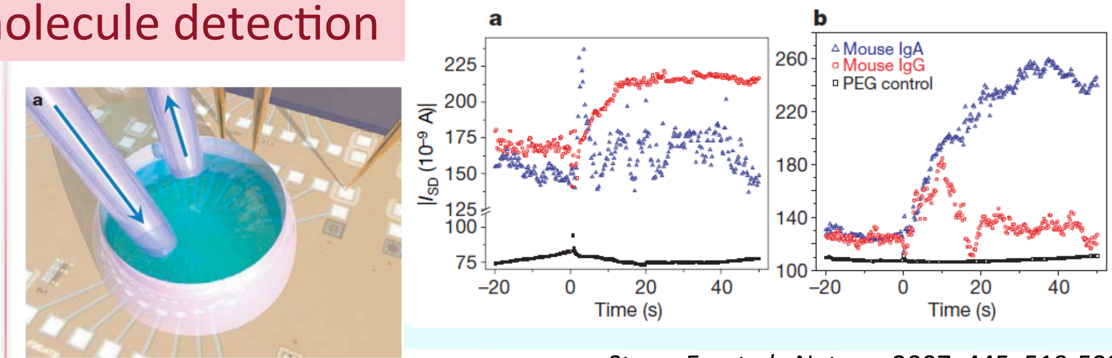

Zhang, G., *et al.*, Nature Nanotech., 2005, 23(10), 1294-1301

## DNA detection




Gao, A., *et al.*, Nano Lett. 2011, 11, 3974–3978

## Small molecule detection




Stern, E., *et al.*, Nature, 2007, 445, 519-522

# Design tools for integrated sensors

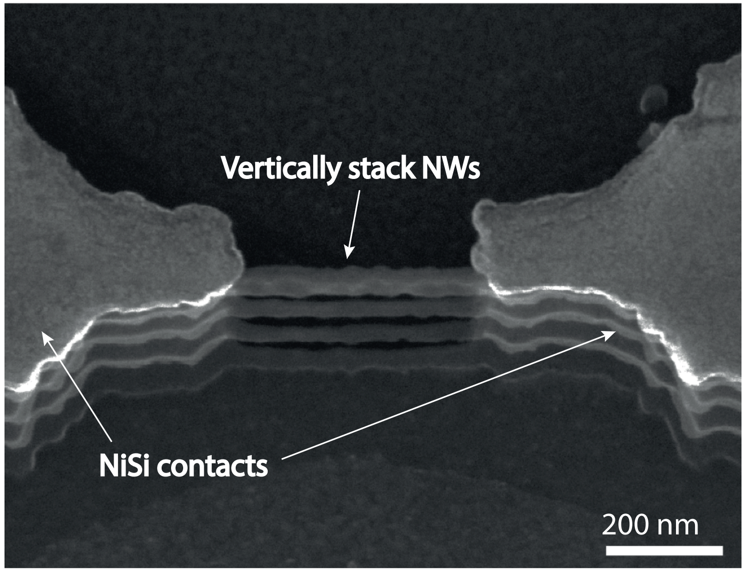
- Layout generation of the sensor masks
- Sensor and electrical front-end co-simulation
  - Under chemical stimuli
- Signal integrity analysis
  - Crosstalk, drift
- Synthesis of regular array structures

# Issues in electrical biosensors

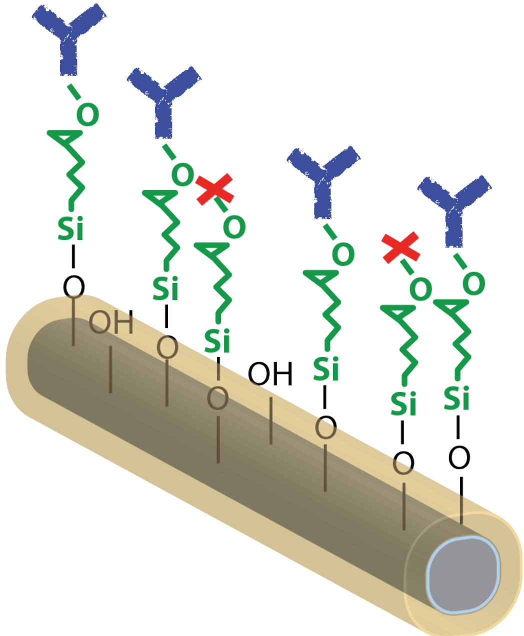
- Dimensions and integrated realization
- Mediated/non mediated reactions
  - Stability of organic mediators
- Electrode nano structuring
  - Enhancing performance
- 3-Dimensional architectures

# Example of fabrication steps

▲SiNWs realized by DRIE and bio-functionalization

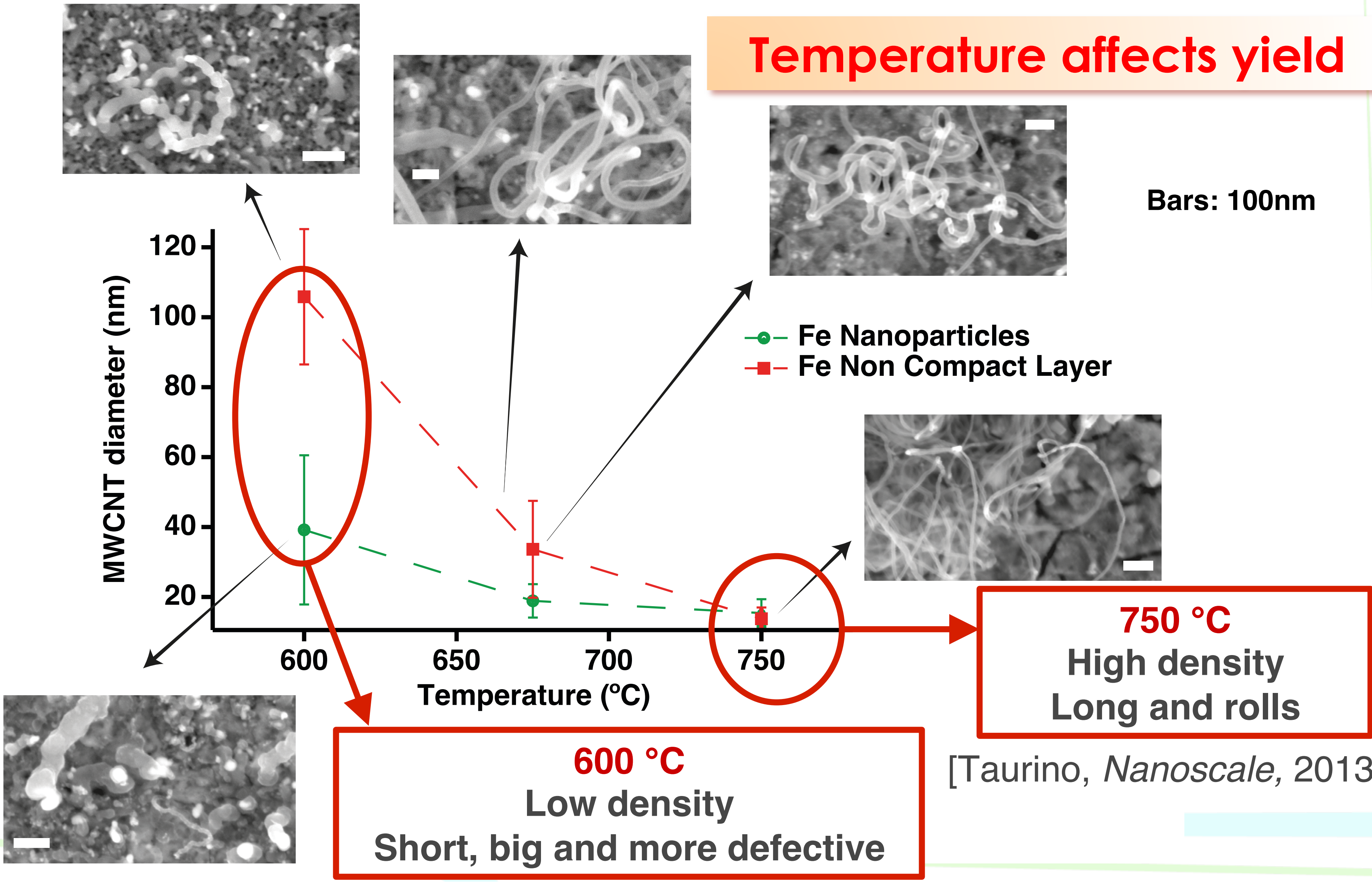



[Courtesy Puppo, EPFL]



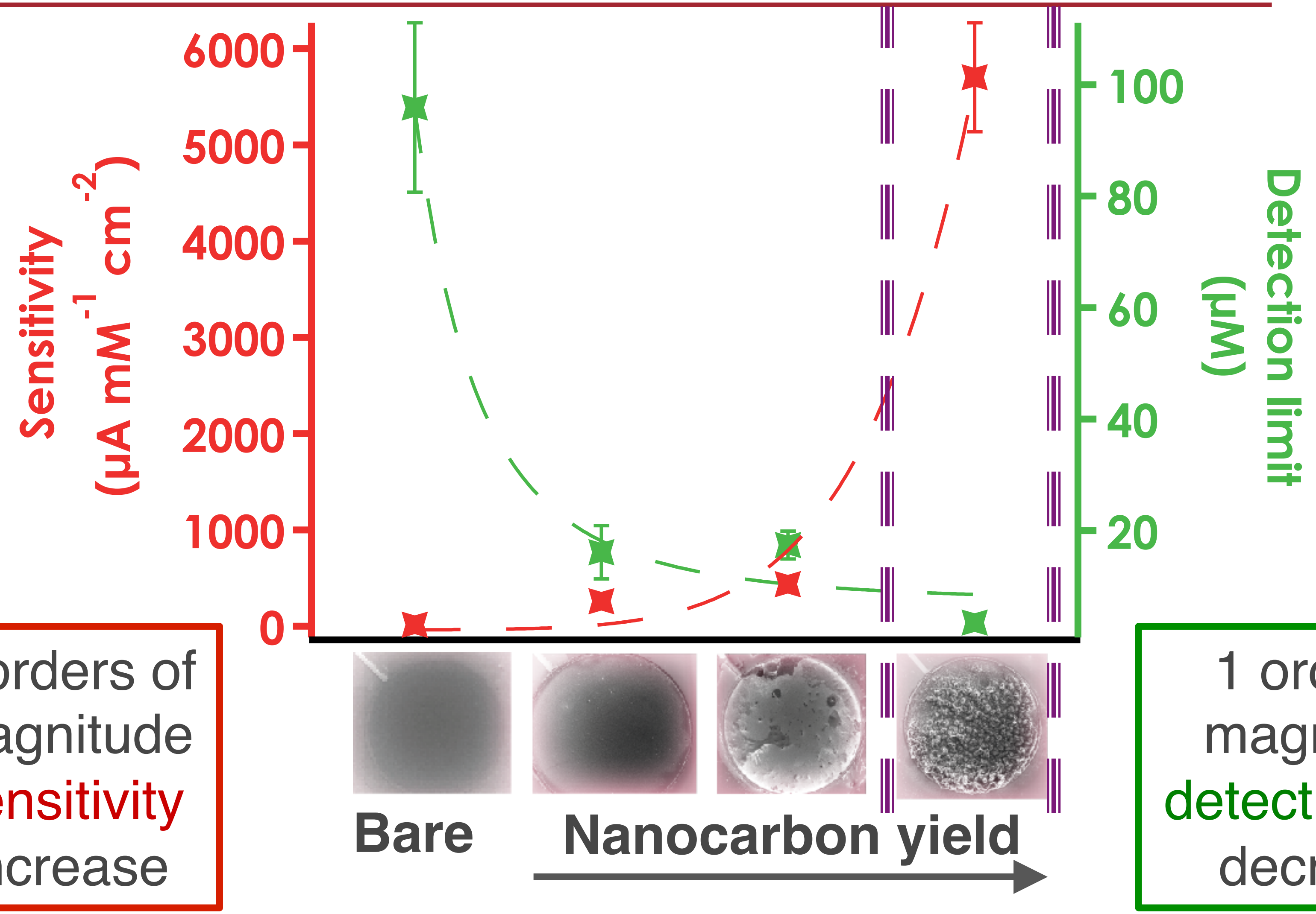
# Nanostructuring: growing CNTs on Si

**Temperature affects yield**




[Taurino, *Nanoscale*, 2013]

# Nanostructuring (Uric Acid)



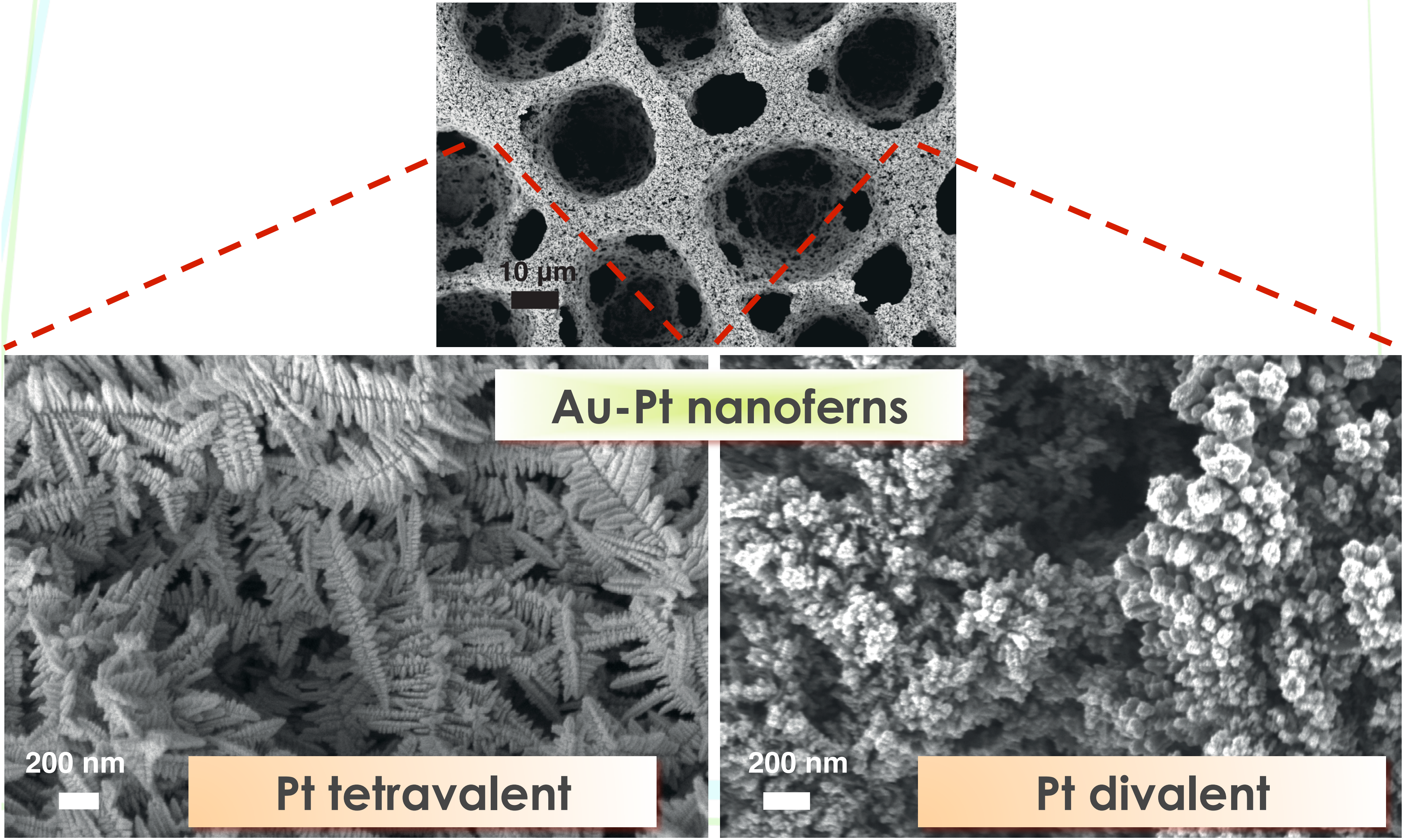

2 orders of magnitude sensitivity increase

1 order of magnitude detection limit decrease

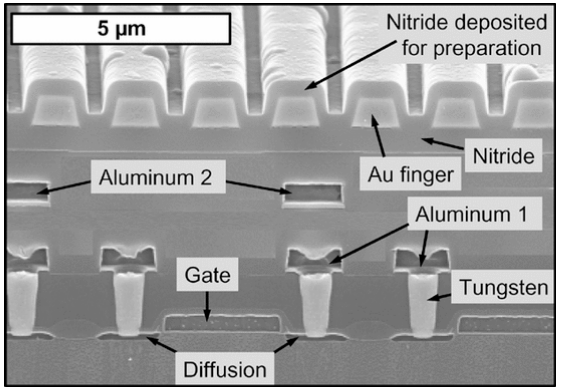


[Taurino, *Nano Letters*, 2014]

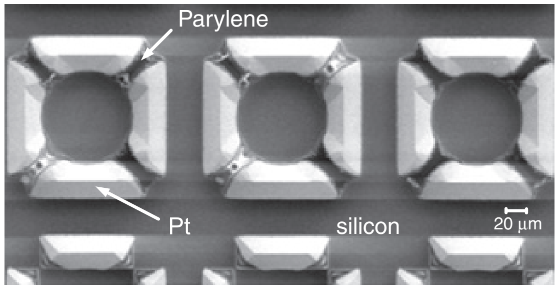
# Nanostructuring: Au-Pt Nanoferns



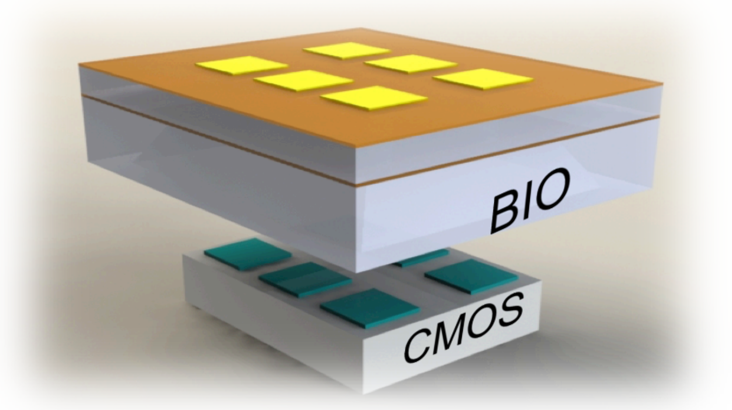
# Monolithic and TSV-based integration

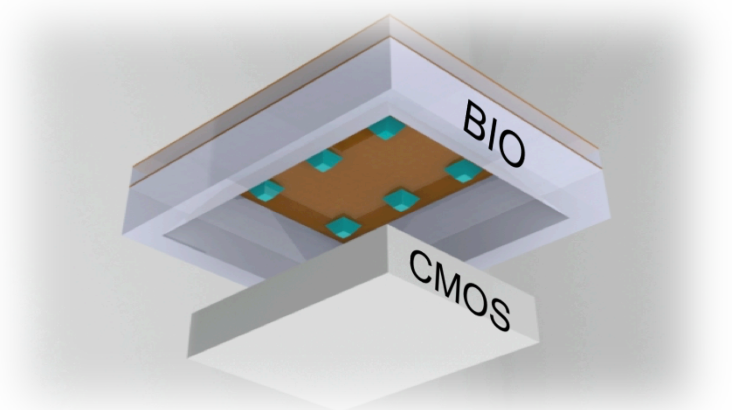



[Schienle et al., JSSC 2004]




[Temiz et al., El Letters 2011]




[Temiz et al., Lab on Chip 2012]

# Key points

- ▲ Electrical biosensors are available for various substances
  - ▽ Still limited use because of predictability
- ▲ Strong potential for future growth
  - ▽ Integration with front-end electronics
  - ▽ Parallel redundant measures
- ▲ Various nano-materials and technologies can be used because of dimensional compatibility

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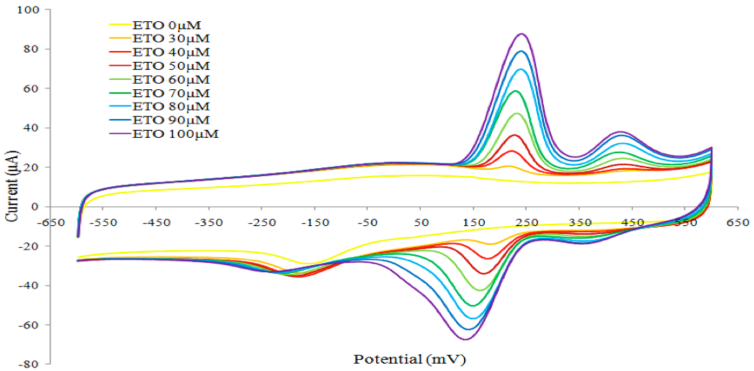
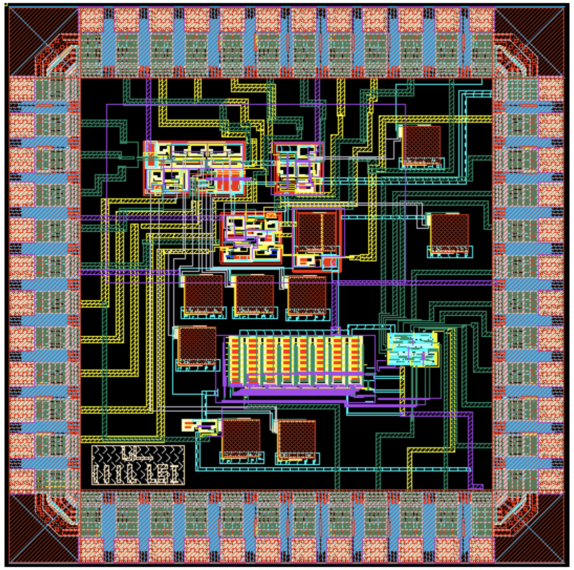
# Circuits and design

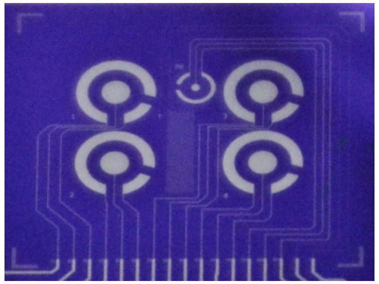
- Electrical readout methods:
  - Impedometric
  - Chronoamperometry
  - Cyclic voltammetry



- Requirements
  - Low noise (drift)
  - Low power (implants)

# Programmable sensing platform



- Multiple sensor integration on silicon
  - Electronic resource sharing
  - Various dynamic ranges
- Reducing Non-Recurring Engineering (NRE)  costs
  - Modular electrode and interface physical design
  - Standard-cell like design
- Several families of medical tests where analyses can be done by sensors with similar structures
  - Possibly various current values and ranges of interest
  - Readout circuit sharing/multiplexing

# Field-programmable sensing array

- Sensor array platform where targets are chosen after silicon fabrication
  - FPGAs are reminiscent of FPGAs
  - Maximal flexibility in application
- Programming FPSAs
  - Selecting sensing mediators in last fabrication step
  - Providing sensing mediators via microfluidics
  - Selecting sensing sites on the field by programming

# Sensor data analysis

- Biosensor integration enables
  - Multiple/simultaneous readout of
    - Same target
    - Different targets
- Data elaboration to enhance result quality
  - Reproducibility
  - False positive/negative
- Majority and threshold logic play an important role in data processing
  - *In situ* data processing

# SW tools for design and operation

- Design tools for sensor subsystems
  - Current DA tools plus sensor design support
- On-line support tools
  - Map clinical requirements to specific bio tests
  - Configure system for sensing operation
- Conformity check
- Redundant checks can increase reliability

# Key points

- ▲ Co-design of electronics and sensing is crucial
  - ▽ Achieve low-power consumption
  - ▽ Achieve small footprint
- ▲ Platform-based design
  - ▽ Modularity of design can reduce NREs
- ▲ Electronic technology can be extended upwards
  - ▽ Monolithic integration
  - ▽ Silicon interposer technologies

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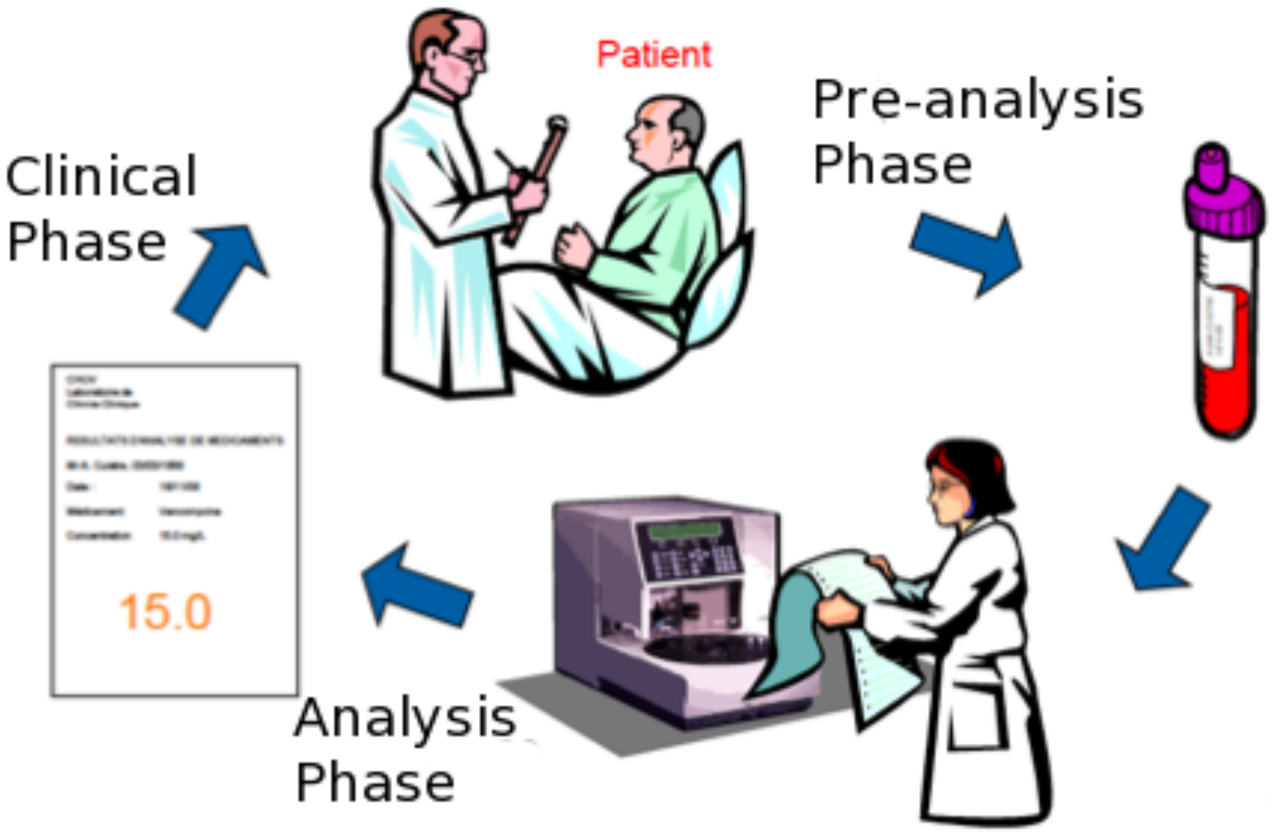
# Therapeutic Drug Monitoring (TDM)

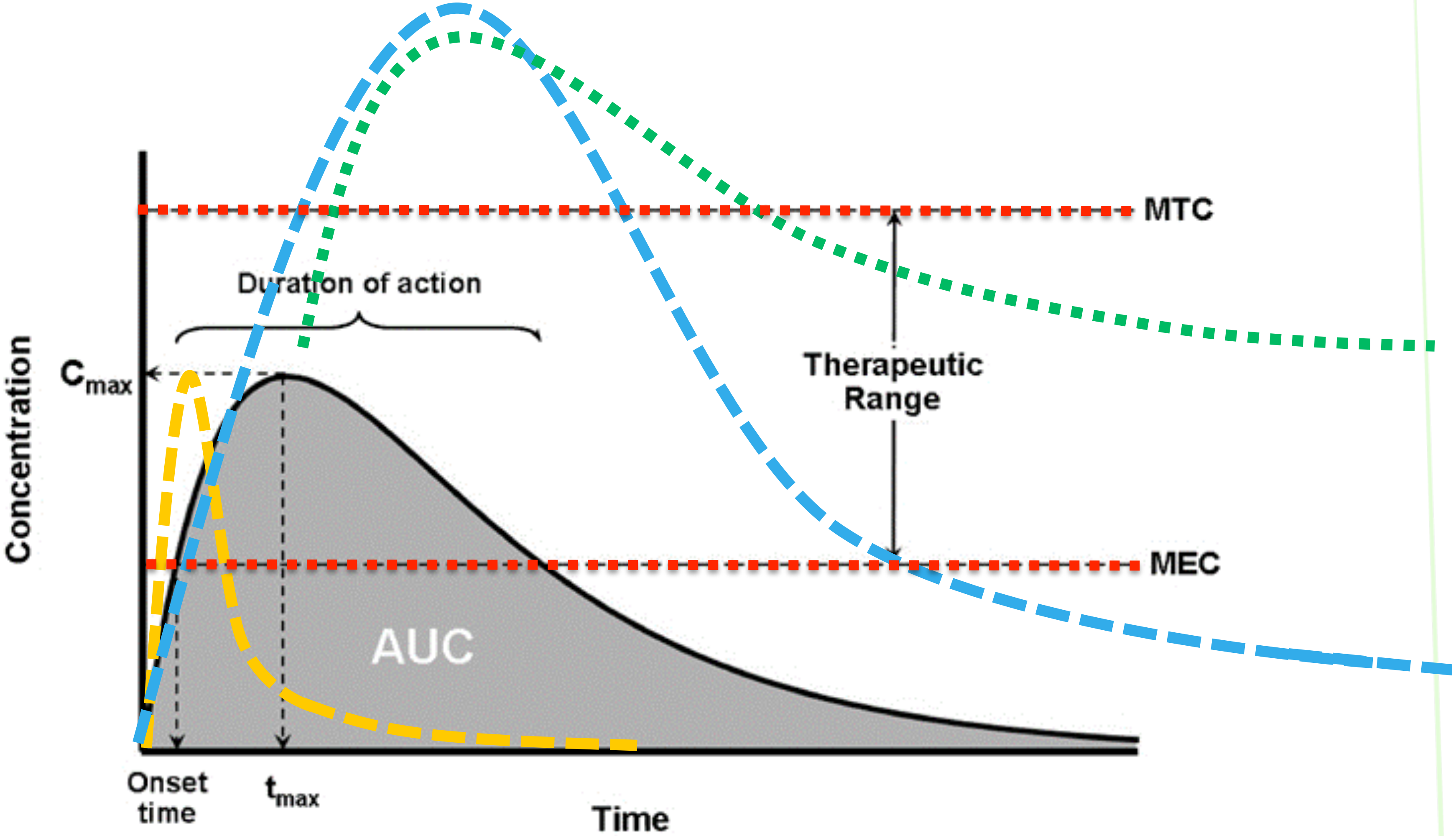
- Drug dosage according to the individual *pharmacokinetic profile*





J. Hiemke / European journal of clinical pharmacology 64.2 (2008): 159-166.

# Drug concentration in blood



# Smart drug administration

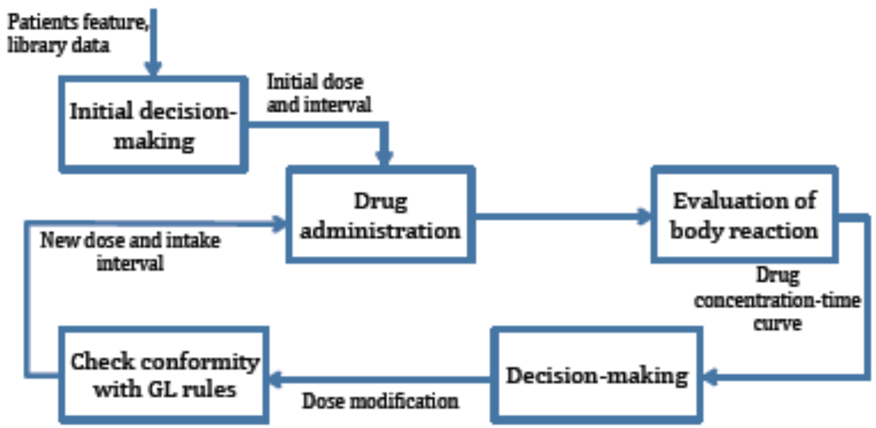
- Policy design:
  - Determine the sequence and dose of the drug
- Predictive models:
  - Extract *system state* from external parameters
- Close-loop models:
  - Measure system state: drug concentration
- Objective:
  - Minimize drug dose/administration
    - subject to drug concentration to be in the permitted band

# System-level challenges

- Correctness:
  - The system must perform its function in any condition
- Security:
  - No medical information leaking to other parties
  - No access from non-authorized sources
- Safety:
  - Under no condition the health-device can be a threat
  - Safety must be guaranteed for both patient and operator
- Dependability:
  - All devices must work long time in possibly harsh condition
  - Graceful degradation mechanisms

# Correctness

- ▲Diagnostic systems
  - ▽Accuracy, linearity, limit of detection
- ▲Drug administration decision support systems
  - ▽Decisions based on acquired data must be correct
  - ▽Life-critical systems

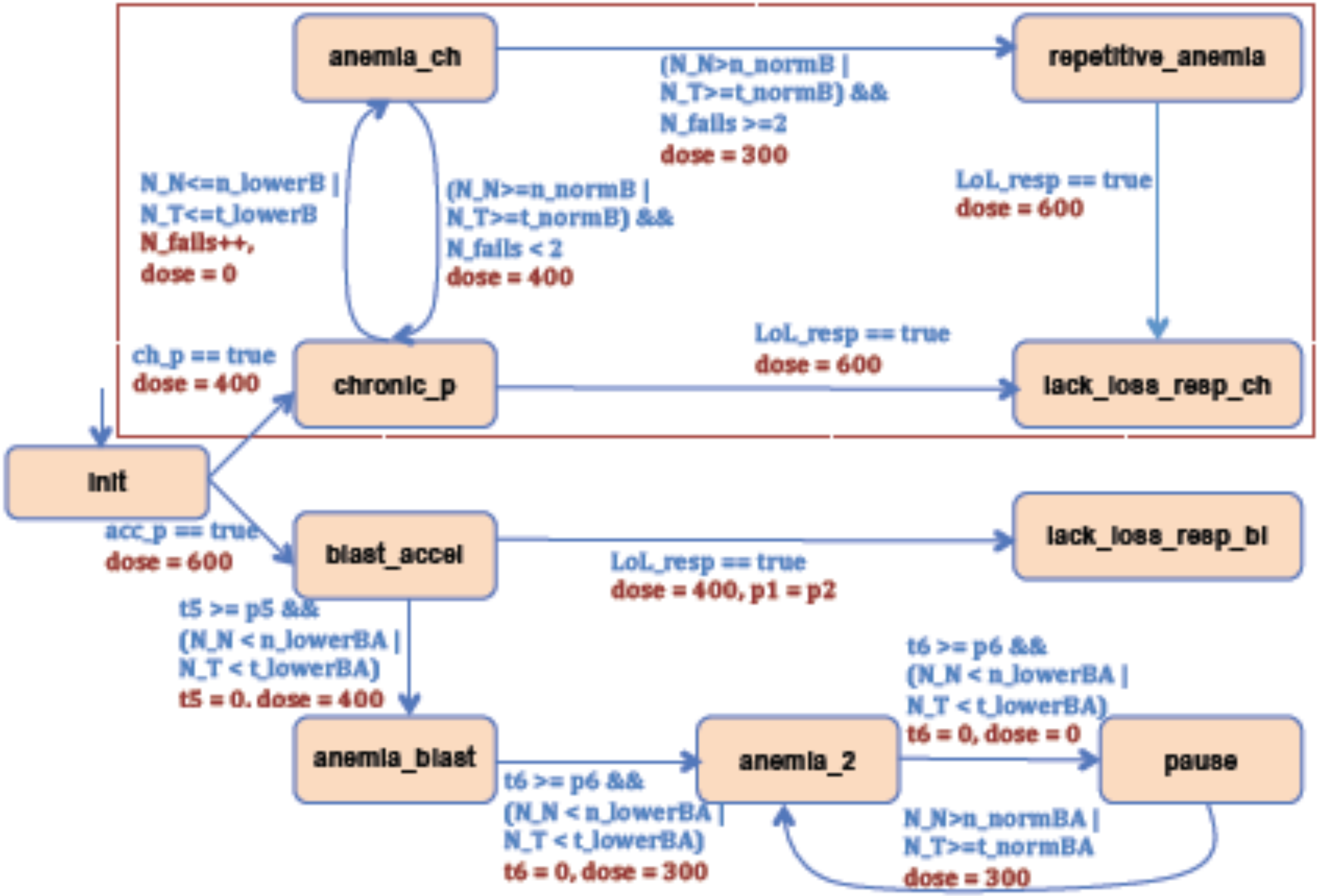



W. You,et al. BioNanoScience, 2013

# The verification problem

- Verify that a therapeutic protocol is
  - Consistent
  - Complete
- Verify that a drug administration control unit is a correct *implementation* of the protocol
  - Model checking

# Formal model of *Imatinib* protocol




 A. Simalastar,et al. International Journal on Artificial Intelligence Tools, vol. 23, no. 3, 2014

# Key points

- Very few protocols have a formal description
  - Corner cases are hazardous for patients
- Personalization of drug dosage is important
  - But still used in few cases
- Modeling human body reaction is critical
  - But often hard to achieve in a deterministic way

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- ▲ **Conclusions**

# Conclusions

- New electronic health systems and services will be enabled by advances in biology and medicine, in combination with progress in electronics
- The rationalization of health care will provide advanced care to a broader audience at lower cost
- Human factors will still be central to decisions in medicine  - decision support will be automated